

Evidence-based Pharmacotherapy of Insomnia and Anxiety in Patients with Chronic Alcohol Use Disorders

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ABSTRACT

Insomnia and anxiety are frequently encountered problems in patients with chronic alcohol use disorders. The use of benzodiazepines and benzodiazepine-receptor agonists in post-withdrawal patients is discouraged due to their abuse potential and cross-reactivity with alcohol, and clinicians should be aware of what alternate medications are available. For the treatment of insomnia, trazodone, low-dose tricyclic antidepressants, gabapentin, and quetiapine can all be used effectively in this population. For common anxiety disorders (panic disorder, generalized anxiety disorder, social anxiety disorder, and posttraumatic stress disorder), selective serotonin reuptake inhibitors, buspirone, venlafaxine, quetiapine, and gabapentin all have varying levels of evidence of efficacy. These medications have their greatest effect when used in conjunction with continued behavioral and other non-pharmacologic therapy.

INTRODUCTION

Alcohol use disorders are known to be frequently comorbid with insomnia, anxiety, and depression.^{1,2} While depression can be difficult to treat in alcoholics, the medications used to treat depressive symptoms in this population are no different than those used in the general population.³ In contrast, the treatment of insomnia and anxiety in alcoholic patients is made particularly challenging by the relative contraindication of benzodiazepines in this population due to their abuse liability.⁴ Clinicians who treat patients with

FOCUS POINTS

- Some antidepressants at low doses (trazodone, tricyclic antidepressants), at least one antiepileptic (gabapentin), and atypical antipsychotics (particularly quetiapine) can all be used to treat insomnia in patients with chronic alcohol use disorders.
- For the treatment of common anxiety disorders in alcohol-dependent patients, there is varying degrees of evidence supporting the use of selective serotonin reuptake inhibitors, venlafaxine, buspirone, quetiapine, and gabapentin.
- Large-scale, placebo-controlled trials assessing the efficacy of common anxiolytics in the treatment of anxiety disorders in alcohol-dependent patients are generally lacking.
- Benzodiazepines and benzodiazepine receptor agonists should be used in patients with alcohol-use disorders only with extreme caution.

alcohol use disorders should be aware of what options are available to treat insomnia and anxiety.

A significant association between alcohol dependence and insomnia has been shown in several community samples.^{5,6} Moreover, disturbed sleep has been shown to be a strong predictor of relapse in alcoholics after detoxification,^{7,8} and alcoholic patients are much more likely to use alcohol to self-medicate for their insomnia.⁸ During acute withdrawal, alcoholics have short and fragmented sleep with long sleep latencies, very small amounts of delta (stages 3 and 4) sleep, and vivid dreams.⁹ Sleep continues to be significantly disrupted during the first month of sobriety and slowly improves over the next few months. Some measures of sleep quality remain

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abnormal at ≥ 14 months after abstinence, with continued decreased delta-wave sleep, increased rapid eye movement (REM) percentage, and increased REM latency.¹⁰

Alcoholism is also frequently comorbid with anxiety disorders. In some patients with a genetic predisposition to an anxiety disorder, ingestion of alcohol can “unmask” anxiety symptoms.¹¹ Other patients with preexisting anxiety disorders frequently use alcohol to self-medicate. The National Comorbidity Study found that in 8,000 respondents with alcohol use disorders in the United States between 15–54 years of age, 37% had at least one anxiety disorder, most commonly social anxiety disorder (18%).¹² Independent community studies from Germany and Australia have reported rates of comorbid anxiety disorders among alcoholic patients of 42.3% and 15%, respectively, with the most common disorders being generalized anxiety disorder (GAD) and specific phobia.^{13,14} Significantly higher degrees of anxiety are found in patients who subsequently relapse within 6 months of initiating abstinence than those who manage to stay sober.¹⁵

This article discusses the alternatives to benzodiazepine treatment in the management of insomnia and anxiety in post-withdrawal alcohol-dependent patients. For the treatment of insomnia in these patients, trazodone, tricyclic antidepressants (TCAs), gabapentin, and quetiapine are commonly used. For anxiety disorders, selective serotonin reuptake inhibitors (SSRIs), buspirone, venlafaxine, quetiapine, and gabapentin can all generally be used with efficacy, depending on the specific type of anxiety disorder.

INSOMNIA

Antidepressants

The sedative properties of some antidepressants, typically at low doses, can be used to treat insomnia in alcoholic patients. Trazodone is the second most common medication used by clinicians for insomnia (after zolpidem), despite the relative absence of convincing evidence of its efficacy in non-depressed patients with insomnia.¹⁶ It is the agent most commonly used by addiction specialists to treat insomnia in alcoholic patients.¹⁷ Trazodone has a relatively benign side-effect profile (most common side effects being drowsiness, dizziness, dry mouth), appears to have few interactions with alcohol,¹⁸ and does not have abuse potential.¹⁹ Some data suggest that tolerance to the sedative effects of trazodone may develop over long-term use.¹⁶ For example, two studies^{20,21} looking at objective measurements of the sedative effects of trazodone show a slight decrease in the total sleep time in subjects using trazodone after week 3 in one study²⁰ and week 4 in the other.²¹ However, further studies are needed to clarify this effect.

A small (n=16), double-blind, placebo-controlled study²² assessing the efficacy of trazodone in improving sleep in post-withdrawal alcoholics found that, after 4 weeks, patients receiving nightly trazodone (50 mg/night, titrated up to 200 mg) had significantly increased sleep efficiency, less frequent night-time awakenings, and increased non-REM sleep percentage, than those receiving placebo. A later double-blind, placebo-controlled study¹⁹ with a larger sample size (n=173) confirmed that trazodone improves sleep quality and overall mental health during its administration. However, the study¹⁹ also found that the patients in the trazodone group had less improvement in the proportion of abstinent days during 3 months of treatment and drank a greater number of drinks per drinking day following the cessation of the medication than the placebo group. Therefore, trazodone was not recommended with confidence for the routine treatment of insomnia in alcohol-dependent patients.

Sedating TCAs can be used at low doses for their anti-histaminergic properties to treat insomnia. For example, doxepin, whose antidepressant effects are typically seen at daily doses of 50–300 mg, has been shown to produce effective hypnotic effects at doses of 1–6 mg/day.^{23,24} At these low doses, doxepin is selective for blocking only histamine (H)₁ receptors and has no effect on serotonin or norepinephrine transporters or muscarinic acetylcholine receptors.²⁵ Selective H₁ blockade is not associated with rebound insomnia, loss of hypnotic efficacy over time, or daytime sedation; these undesirable effects of many “antihistamine” medications are largely due to their actions on muscarinic, cholinergic, and adrenergic receptors.^{25,26} Because muscarinic receptors are not affected at such low doses, the anticholinergic side effects of confusion, dry mouth, blurred vision, constipation, and urinary retention, which are commonly associated with TCAs, are not seen with low dose doxepin. TCAs also have the benefit of not producing euphoria as a side effect, not causing physical tolerance or dependence, and not being controlled substances.²³ TCAs should be used with caution in alcohol-dependent patients; even mild overdoses can cause cardiotoxicity or severe orthostatic hypotension and can be fatal, something to be wary of in a population that is at an increased risk for suicide attempts. Moreover, TCAs can lower the seizure threshold, so they should be used with caution in patients undergoing alcohol withdrawal.

SSRIs are generally not used to treat insomnia, as they can frequently worsen sleep and increase the number of nighttime awakenings.²⁴ Nefazodone, an antidepressant with a similar structure to trazodone, has some sleep-promoting properties, but it is rarely used today because of its risk of serious hepatic toxicity.

Gabapentin

Gabapentin has recently been gaining favor for the treatment of alcohol dependence and alcohol-related insomnia. Gabapentin is an antiepileptic medication that has a relatively

benign side-effect profile, little abuse potential, and does not affect the metabolism or excretion of other medications. Gabapentin has been studied for alcohol-related insomnia during both acute withdrawal and after several weeks of abstinence. During acute withdrawal, gabapentin was shown to be superior to lorazepam in reducing nighttime insomnia and daytime sleepiness among subjects with a history of repeated withdrawal episodes.²⁷ In a preliminary non-blinded, uncontrolled study of post-withdrawal insomnia, Karam-Hage and Brower²⁸ showed that 15 alcohol-dependent patients had improved sleep quality as per the Sleep Problems Questionnaire (SPQ) with an average gabapentin dose of 953 mg/day.

In another non-randomized, non-blinded, uncontrolled study²⁹ (n=50) comparing gabapentin with trazodone for the treatment of post-withdrawal insomnia in patients with alcohol dependence, both medications were shown to improve sleep quality, as per the SPQ, although gabapentin improved sleep quality significantly more than trazodone and was associated with less sedation the next day. However, in a recent double-blind, placebo-controlled pilot trial³⁰ (n=21) of post-withdrawal alcohol-dependent subjects, the same authors found no significant difference in the sleep quality of the gabapentin versus placebo group, as measured by the SPQ, sleep diary parameters, and polysomnography parameters. Of note, gabapentin significantly delayed the onset of relapse to drinking in this study.

Quetiapine

Of the typical and atypical antipsychotics, quetiapine is the one most commonly used clinically in patients with alcohol use disorders to reduce cravings and promote sleep. A small-scale retrospective review³¹ of male alcoholic patients at a Veterans Administration (VA) hospital showed that, in patients with difficulty initiating sleep, quetiapine initiated at a dose of 25–50 mg and titrated up to 200 mg increased the total number of days of abstinence and significantly lowered the rate of hospital admissions. The study did not comment on sleep differences between the two groups. Another retrospective chart review³² of data from patients admitted to a 28-day residential rehabilitation program showed significant improvement in insomnia in alcoholic patients given quetiapine. In an open-label pilot trial³³ of 28 dually diagnosed alcoholics, quetiapine significantly decreased middle and late insomnia. A randomized control trial³⁴ by the Department of Veterans Affairs to study the use of quetiapine for insomnia during alcohol abstinence is currently recruiting participants. Of note, the use of quetiapine as a drug of abuse has been rising; it is the antipsychotic most commonly implicated in the literature in case reports of antipsychotic abuse.³⁵ It has several street names, such as “quell,” “Susie-Q,” and “baby heroin.”

ANXIETY

Any of the common anxiety disorders (panic disorder, GAD, social anxiety disorder, and posttraumatic stress disorder [PTSD]) can be comorbid with alcohol abuse or dependence. Below, evidence regarding treatment will be reviewed by disorder. When assessing these disorders in the context of alcoholism, it is important to distinguish them from transient anxiety states related to alcohol intoxication or withdrawal, as these may improve with abstinence alone. The best way to approach this task is by observation of the patient during a period of abstinence, generally after 3 or 4 weeks of sobriety for patients recovering from chronic alcohol use.³⁶

Panic Disorder

Several types of antidepressants, including SSRIs, TCAs, monoamine oxidase inhibitors (MAOIs), and venlafaxine, have been shown to be effective in the treatment of panic disorders in patients without substance use disorders, but they have not been studied systematically for use in patients with alcohol or other substance use disorders. Given the unfavorable side-effect profiles of TCAs and MAOIs, SSRIs and venlafaxine are logical choices among antidepressants for the treatment of panic disorder in patients in remission from alcohol.¹¹ SSRIs have a relatively benign side-effect profile, are safe in overdose, and have little abuse potential. To avoid increased anxiety with the initial activation associated with SSRIs, they should be started at a low dose and titrated upwards slowly. Patients should be monitored for relapse in the 4-to-6-week window it takes for the SSRIs to have an effect. As these medications are metabolized by the liver, lower doses should be used in chronic alcoholic patients who have compromised liver function.³⁷ Venlafaxine, a serotonin-norepinephrine reuptake inhibitor, is approved by the US Food and Drug Administration for the treatment of panic disorder³⁸; however, trials of its use in alcohol-dependent patients are lacking.

Gabapentin may be a novel alternative to SSRIs in the treatment of severe panic disorder. In a double-blind, placebo-controlled study (n=103), gabapentin (dosed from 600–3,600 mg/day) was not found to be more effective than placebo in reducing scores on the Panic and Agoraphobia Scale (PAS).³⁹ However, in the severely ill subset of patients with baseline PAS \geq 20, the patients treated with gabapentin showed significant improvement in PAS scores. Gabapentin has not been studied for treatment of panic disorder in alcoholic patients; however, it has a favorable risk-benefit profile and may be a good option for alcoholic patients with severe panic symptoms for whom SSRIs or venlafaxine are not good options or are ineffective.

GAD

Diagnosis of GAD in patients with substance abuse disorders is challenging, as many symptoms of intoxication and withdrawal, such as anxiety, restlessness, difficulty concentrating, fatigue, and sleep disturbance, are similar to the symptoms of GAD. Of the anxiolytic medications, buspirone has been studied most extensively for treatment of GAD in alcoholic patients.⁴⁰ This is a generally well-tolerated medication with a favorable side-effect profile (most common side effects being dizziness, nausea, headache, nervousness, lightheadedness, and insomnia). Patients given buspirone (average daily dose 20 mg/day) in a double-blind, placebo-controlled trial⁴¹ (n=50) in outpatients with mild-to-moderate alcohol abuse demonstrated decreased scores on the Hamilton Rating Scale for Anxiety (HAM-A) as well as lower discontinuation rate and decreased cravings. In another trial⁴² evaluating 51 patients with dual diagnoses of alcohol abuse or dependence and GAD, the buspirone treatment group had decreased overall anxiety, less number of days desiring alcohol, and overall clinical global improvement. However, in a double-blinded, placebo-controlled study⁴³ (n=67) of alcohol-dependent patients with high levels of generalized anxiety in a Veteran's Administration hospital, there was no significant difference on scores between the treatment and placebo groups on the HAM-A or the Spielberger State Anxiety Scale. Lastly, in a randomized, 12-week, placebo-controlled trial,⁴⁴ buspirone was found to be associated with reduced anxiety, greater retention rate, a slower return to heavy alcohol consumption, and fewer drinks during the follow-up period compared to placebo. Anxiolytic effects with this medication may only be seen at relatively higher doses (above 30 mg/day) after 2–4 weeks of treatment.⁴⁵

SSRIs, TCAs, venlafaxine, and some anticonvulsants are also effective in treating symptoms of GAD in the general population. However, trials studying these medications in the treatment of GAD specifically in alcoholic patients are lacking. Based on side effects, metabolic profiles, and data from non-alcoholic patients, buspirone, SSRIs, and venlafaxine are likely the most reasonable choices in alcohol-dependent patients for the treatment of GAD.

Social Anxiety Disorder

Kessler and colleagues⁴⁶ found the rate of comorbidity of social anxiety and alcohol abuse to be 22%. Patients with social anxiety disorder often use alcohol to self-medicate and ease anxiety in social situations. In the general population, MAOIs (phenelzine, brofaromine, and moclobemide), SSRIs (sertraline and fluvoxamine), benzodiazepines (clonazepam), and one antiepileptic (gabapentin), have been shown to be effective in treating social anxiety in placebo-controlled trials.⁴⁷ Buspirone is not effective in treating social anxiety.⁴⁸ Placebo-controlled

trials studying these medications in patients with comorbid alcohol use disorders and social anxiety are lacking, with the exception of one study⁴⁹ examining the use of paroxetine. In this 8-week, double-blind, placebo-controlled trial (n=18), alcohol-dependent patients in the treatment group (paroxetine titrated to 60 mg/day) showed a significant improvement in social anxiety symptoms (as per the Clinical Global Index and the Liebowitz Social Anxiety Scale) by week 6 of the trial. Of note, no significant difference on any of the quantity/frequency measures of alcohol use was seen between the two groups.

PTSD

PTSD is associated with a greatly increased risk of alcohol dependence.⁵⁰ SSRIs have been widely shown to be successful in the treatment of PTSD in the non-substance-abusing population. In a preliminary open-label trial of sertraline in patients with comorbid alcohol-dependence and PTSD, PTSD symptom scores (per the Impact of Event Scale) and average number of drinks during the follow-up period decreased, while the number of days of abstinence increased.⁵¹ In a follow-up randomized, placebo controlled trial (n=94) of sertraline in PTSD patients with comorbid alcohol-use disorders, the same authors⁵² found a significant decrease in alcohol use in both the treatment and placebo groups. Of note, in this study, a subgroup of patients with less severe alcohol dependence and early-onset PTSD had significantly fewer drinks per drinking day with sertraline treatment than other groups.

Several atypical antipsychotics, including risperidone,⁵³ olanzapine,⁵⁴ and quetiapine,⁵⁵ have been shown to be effective as adjunctive agents to SSRIs in alleviating PTSD symptoms in the general population. However, they have not been studied in patients with co-morbid PTSD and alcohol-use disorders. In a retrospective study³¹ assessing quetiapine treatment in alcohol-dependent patients in a VA hospital, 90% of whom had PTSD, the authors found a decrease in the number of detoxifications needed per year, increase in the total number of abstinent days, and longer mean time to relapse in patients receiving quetiapine for sleep. These improvements were attributed at least partially to reduction in PTSD symptoms from quetiapine.

Benzodiazepines and Benzodiazepine-Receptor Agonists

The use of benzodiazepines in alcoholic patients merits special discussion. These medications are frequently used to treat anxiety and insomnia in the general population. However, except in the treatment of acute alcohol withdrawal, use of these medications in patients with alcohol use disorders is generally discouraged.⁴ They share a similar mechanism of action on γ -aminobutyric acid receptors to alcohol and have a high abuse potential.⁵⁶ Even in patients without substance

use problems, they are generally recommended only for short-term usage and in conservative dosages.⁵⁷

Benzodiazepine receptor antagonists (BzRAs), like zolpidem and zaleplon, present an interesting scenario in the treatment of insomnia in alcoholic patients. These medications are generally well tolerated, and studies have shown that they do not cause tolerance or dependence at physiologic doses over short-term (4-week) nightly use⁵⁸ or long-term (12-week) non-nightly use.⁵⁹ A very large percentage of patients who use BzRAs for primary nighttime insomnia do not go on to develop dependence or to abuse the drug in the daytime for non-therapeutic reasons.⁶⁰ In 2002, a systematic review of all published case studies of BzRA dependence found only 36 cases of zolpidem dependence and 22 cases of zopiclone dependence, almost all of which involved former drug or alcohol abusers or patients with other recognized psychiatric disorders.⁶¹ This relatively low number of published cases of dependence was in marked contrast to the much higher incidence of dependence known with benzodiazepines. The authors concluded that zolpidem and zopiclone are relatively safe medications, but “extreme caution” should be utilized when prescribing them to patients with a history of substance abuse, dependence, or other psychiatric illness.

It is worth mentioning that withholding benzodiazepines or BzRAs from all post-withdrawal alcoholic patients as a rule may not be an optimal strategy. According to Lejoyeux and colleagues,⁴ an anxiolytic agent might help to improve the quality of life and adherence to treatment in patients with severe anxiety. A recent prospective study⁶² monitoring 545 patients with comorbid anxiety and alcohol-use disorder receiving benzodiazepines over 12 years showed that benzodiazepine usage did not predict recovery or relapse. However, the authors were cautious in generalizing their results to all patients or the set of patients who present for addiction treatment. The judicious use of benzodiazepines in a given patient should be decided on a case-by-case basis after a careful assessment of the alternatives as well as the risks and benefits involved.

CONCLUSION

The management of insomnia and anxiety in the alcohol-dependent population can be challenging. With the relative contraindication of benzodiazepines and BzRAs, clinicians have to turn to alternative medications to treat these symptoms. It is important to keep in mind that none of the medications discussed above are FDA-approved for treatment of insomnia or anxiety disorders in alcohol-dependent patients. Moreover, they have their greatest effects when used in conjunction with continued behavioral and non-pharmacologic therapy.⁶³ Continued research is needed to further identify the safety and efficacy of these medications in this unique patient population. **PP**

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